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FULL-TEXT ARTICLE

Fusion of a signal sequence to the interleukin-1 beta gene directs the protein from cytoplasmic accumulation to extracellular release.

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Interleukin (IL)-1 differs from most other cytokines by the lack of a signal sequence, which results in the retention of the immature proform intracellularly (i.c.). Several cell types have the capacity to produce IL-1, but release has been shown to be restricted predominantly to monocytes/macrophages and associated with apoptosis of the producer cell. These features have limited the studies on IL-1 in early T cell-APC interactions. To develop a model for studying the biological effects of IL-1 beta release during long-lasting immune responses, we have established cells transfected with IL-1 beta cDNA constructs. To construct a hybrid gene for IL-1 beta release, the signal sequence from the related IL-1 receptor antagonist was fused to the gene encoding the 17-kDa mature form of IL-1 beta. A murine fibroblast cell line was transduced with retroviral technique and analyzed for the expression of human IL-1 beta, with or without a signal sequence (ssIL-1 beta and IL-1 beta, respectively). The fibroblasts transduced with either IL-1 beta or ssIL-1 beta expressed similar levels of human IL-1 beta mRNA. High levels of IL-1 bioactivity were recorded in freeze-thaw extracts from cells expressing the IL-1 beta protein i.c., and in supernatants of ssIL-1 beta-transduced cells, which indicates that the initial formation of a proform of IL-1 beta is not required for correct folding of the protein. Treatment of ssIL-1 beta-transduced cells with Brefeldin A (BFA), an inhibitor of protein transport in the endoplasmatic reticulum, induced accumulation of the protein i.c. BFA treatment did not affect IL-1 beta-transduced cells, while lipopolysaccharide-activated human monocytes increased the secretion of IL-1 beta. Cytoplasmic staining of single cells demonstrated that expression of the ssIL-1 beta gene directed the protein to a perinuclear Golgi-like compartment, whereas cells transduced with IL-1 beta cDNA showed a diffuse cytoplasmic distribution pattern. Secretion of IL-1 beta from human monocytes was under certain conditions accompanied by cell death. In contrast, in the fibroblast cell line transduced to secrete IL-1 beta, no accompanying cell death could be detected. Gene targeting of IL-1 to the secretory or cytoplasmic pathway may be useful for elucidating the role of IL-1 in T cell-APC interactions, avoiding cell death of the producer cells.

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